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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,459	11/07/2001	David L. Lewis	Mirus.030.04	3774

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MIRUS CORPORATION
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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
10/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/007,459	LEWIS ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11 and 13-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed July 25, 2007.

Claims 11 and 13-18 are pending in the instant application.

Claims 11 and 13-18 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Declaration under 37 C.F.R. §1.132

Applicant's Declaration under 37 C.F.R. §1.132 filed July 25, 2007 is acknowledged, has been made of record, and has been fully considered by the Examiner.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed April 24, 2007, claims 11, 13, 14, 16, and 17 were rejected under 35 U.S.C. 102(b) as being anticipated by Desjardins et al. (Journal of Pharmacology and Experimental Therapeutics, 1996 Vol. 278:1419-1427). **This rejection is withdrawn** in view of Applicant's Remarks filed July 25, 2007. It is noted that in the Office Action mailed April 24, 2007, the Examiner interpreted the ribozyme comprised in pyrogen-free isotonic saline solution disclosed by Desjardins et al. to be an amphipathic solution, thus reading on the ribozyme complex requirement of the instant claims. Applicants argue that Desjardins et al. do not teach injection of a

double-stranded RNA complex. Specifically, Applicants argue that the pyrogen-free isotonic saline solution does not contain an amphiphatic compound. Applicant's arguments have been considered and found persuasive. The Examiner agrees that the pyrogen-free isotonic saline solution disclosed by Desjardins et al. does not contain an amphipathic compound. Therefore, Desjardins et al. do not teach injection of a double-stranded RNA complex to parenchymal cells *in vivo* as claimed.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed April 24, 2007, claims 11 and 13-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmer, A. (Methods, 1999 Vol. 18:286-295, made of record in the previous Office Action mailed August 24, 2005) in view of Vaish et al. (Nucleic Acids Research, 1998 Vol. 26:5237-5242, made of record in the previous Office Action mailed July 25, 2006), and Zhang et al. (Human Gene Therapy, 1999 Vol. 10:1735-1737, made of record in the previous Office Action mailed August 24, 2005). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed April 24, 2007.

Response to Arguments

In response to this rejection, Applicants argue that Zimmer et al. teach an injection volume of 5 nmol/5 ml/kg. Applicants contend that since an average mouse weighs about 25 grams, the volume taught by Zimmer et al. equates to 0.125 ml or 125 μl per mouse. Applicants argue that this injection volume is insufficient to cause vessel

permeability in the liver following injection into the tail vein as evidenced by the Declaration under 37 C.F.R. §1.132 filed July 25, 2007. It is noted that the Declaration filed under 37 C.F.R. §1.132 discusses the effect of injection volume on vessel permeability in liver tissue cells following tail vein injection, as measured by nucleic acid delivery. The Declaration teaches that increased permeability is evidenced by delivery and expression of the luciferase gene in target tissue liver cells. Specifically, the Declaration alleges that, "For injection into the tail vein, volumes less than 1.2 ml did not result in increased permeability of vessels in the liver tissue" as measured by nucleic acid delivery (see Declaration under 37 C.F.R. §1.132 filed July 25, 2007, at second page).

Applicant's arguments and Declaration under 37 C.F.R. §1.132 have been fully considered, but are not found persuasive. First, the issue is that Applicant's Specification at page 5, last paragraph discloses, "Permeability is defined here as the propensity for macromolecules such as polynucleotides to move through vessel walls and enter the extravascular space". Zimmer et al. teach antisense nanoparticle complexes were injected into the tail vein at 5 nmol/5 ml/kg. Given the definition of "permeability" in the instant specification, the Examiner is interpreting that the 5 nmlo/5 ml/kg injection volume increased permeability within the target tissue since the ribozyme complex moved through the vessel walls of the vein and entered the extravascular space, ultimately reaching the liver.

Applicant's Declaration suggests that, based on luciferase expression studies, volumes less than 1.2 ml do not result in increased permeability of vessels in the liver

tissue. The Examiner has considered Applicant's Declaration, but is unsure how a measurement of nucleic acid expression is at all correlative with a measurement of permeability of vessels. In fact, Applicant's Specification, at pages 5 and 6 discloses, "One measure of permeability is the rate at which macromolecules move through the vessel wall and out of the vessel." "Another measurement of permeability is the lack of force that resists the movement of polynucleotides being delivered to leave the intravascular space". Given this disclosure, it is unclear how nucleic acid expression studies are directly correlated with permeability of vessels, increased or otherwise. While it does appear that volumes less than 1.2 ml did not express high levels of the luciferase gene, this may not be necessarily due to the fact that permeability of the vessel was not increased. This result could be due to the fact that injected volumes of less than 1.2 ml do not contain enough plasmid encoding the luciferase gene (per volume) to result in a detectable level of expression, for example.

Second, the Declaration concerns results regarding gene expression studies using plasmid DNA encoding the luciferase gene, where the claims are drawn to double stranded oligonucleotides that inhibit gene expression. It is likely that plasmid DNA encoding the luciferase gene is much larger (in nucleobases) than the double stranded oligonucleotide of Applicant's invention. Thus, one of ordinary skill in the art would believe that plasmid DNA encoding the luciferase gene would move through vessel walls at a much different rate than the double stranded oligonucleotide of Applicant's claims. Therefore, one of ordinary skill in the art would not accept the gene expression

and alledged permeability results presented in Applicant's Declaration as correlative with the gene inhibition and permeability requirements of Applicant's claimed invention.

Applicants also argue that the previous Office Action mailed April 24, 2007 states that, "pressure against the vessel walls would inherently be increased because the needle used to delivery the oligonucleotide complexes with the positive and negative charges polymers is external to the tail vein". Applicants contend that the claim clearly recites that it is the volume of the injected solution and not the needle which increases permeability in the target tissue.

Applicant's arguments and contentions have been fully considered, but are not found persuasive because contrary to Applicant's contention, the claim does not recite that it is the volume of the injected solution and not the needle which increases permeability in the target tissue. For example, claim 13 requires that increasing the permeability of the vessel consist of **increasing pressure against vessel walls**. Clearly, the needle used to inject the solution into the tail vein increases pressure against vessel walls since the needle is external to the tail vein. Furthermore, claim 17 requires that increasing the pressure consists of **increasing volume of fluid within the vessel**. Clearly, the use of the needle to administer the solution to the tail vein would increase the volume of fluid within the vessel because whatever the amount of fluid injected would be more than what was otherwise present in the vessel already.

In sum and in conclusion, the Examiner has fully considered Applicant's arguments, contentions, and Declaration under 37 C.F.R. §1.132 filed July 25, 2007, however, none of these have not been found persuasive. Therefore, claims 11 and 13-

18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmer, A., in view of Vaish et al., and Zhang et al.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent

Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

tcg
September 25, 2007

/Sean McGarry/
Primary Examiner
AU 1635